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pK_{R+} Values for Pyridinium Cations

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ABSTRACT

Literature data for nucleophilic addition at C-4 of C-3 substituted 1-methylpyridinium cations are evaluated. It is shown that sufficient data are available to allow the confident evaluation of a linear free energy relationship for the equilibration of these cations with their C-4 hydroxide adducts (pseudobases) in aqueous solution: $pK_{R+} = -8.5\ (\pm 0.4)\ \sigma_p^- + 20.5\ (\pm 0.5)$ This allows the prediction of $pK_{R+} = 20.5$ for pseudobase formation at C-4 of the 1-methylpyridinium cation. A less confident estimate of $pK_{R+} = 18.2$ at C-2 of this cation is also made.

The equilibration of heteroaromatic cations with their pseudobases (hydroxide adducts) in aqueous solution is a well established phenomenon in heterocyclic chemistry.[1,2] This process can be expressed by equation [1], for which an equilibrium constant K_{R+} can be defined as in equation [2]. This equilibrium constant has the form of a Brønsted acid ionization constant, and the cation-pseudobase equilibration is usually described in terms of a pK_{R+} value.

$$R^+ + H_2O \rightleftharpoons ROH + H^+ \qquad [1]$$

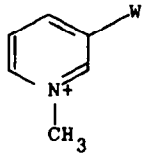
$$K_{R+} = \frac{[H^+]\,[ROH]}{[R^+]} \qquad [2]$$

Accurate pK_{R+} values are now available for a large number of heterocyclic cations.[2,3] However, for many simple species, such as the N-methyl pyridinium, quinolinium and isoquinolinium cations, the pK_{R+} values are sufficiently large that they are not readily accessible by the direct measurement of simple acid-base equilibrations in aqueous solutions. In such cases, indirect methods must be sought for the evaluation of pK_{R+} values. For the N-methylisoquinolinium cation, $pK_{R+} = 16.29$ was evaluated[4,5] by use of a basicity function in basic aqueous dimethyl sulfoxide solutions. However, the application of this method to other heteroaromatic cations, is severely limited by competing irreversible reactions in strongly basic solutions. Such is the

case for the N-methylquinolinium cation, which undergoes rapid disproportionation and condensation reactions in aqueous base.[6,7] This cation also has two potential sites for pseudobase formation, since nucleophilic addition is possible at both C-2 and C-4.

pK_{R+} values are quite sensitive to the nature of substituents on ring carbon atoms of heteroaromatic cations.[3] The development of linear free energy relationships often allows the extrapolation of these relationships to provide accurate estimates of pK_{R+} values for cations for which cation-pseudobase equilibration is not directly accessible. For example, the above quoted pK_{R+} value for the N-methylisoquinolinium cation was subsequently confirmed via a linear free energy relationship that was developed for the substituent dependence of pK_{R+} for C-4 substituted N-methyl isoquinolinium cations.[8] Linear free energy relationships for pseudobase formation at each of C-2 and C-4 in N-methyl quinolinium cations bearing substituents at C-3, have been extrapolated to allow the evaluation of pK_{R+} = 15.4 for hydroxide ion addition at C-2 and pK_{R+} = 17.4 at C-4 in the parent N-methylquinolinium cation.[9]

At the present time, there seem to be no quantitative estimates available of pK_{R+} for the N-methylpyridinium cation, which is susceptible to pseudobase formation at both C-2 and C-4. In fact, there are very few pyridinium cations for which reliable pK_{R+} values are available.[3] The C-3 substituted pyridinium cations (1) are of particular interest, because of their close relationship to the biologically important nicotinamide cation coenzymes. However, in these species there are three non-equivalent sites for nucleophilic attack: C-2, C-4 or C-6. Furthermore, these species are well known to be very susceptible to a variety of ring-opening and disproportionation reactions in aqueous base,[2] so that the evaluation of accurate pK_{R+} values and the specific assignment of these values to hydroxide attack at C-2, C-4 and C-6 is not a simple matter.



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The present work addresses the evaluation of the sparse data that are currently available in the literature on equilibrium constants for pseudobase formation by pyridinium cations. These data are then coupled with equilibrium constants for the addition of other nucleophiles to pyridinium cations, and also with linear free energy relationships that have been developed to relate the susceptibility of a variety of classes of heteroaromatic cations to hydroxide ion attack and to reduction by 1-benzyl-1,4-dihydronicotinamide. As a result of these deliberations, it is shown that a reasonably confident estimate can be made of pK_{R+} for hydroxide ion addition to C-4 of the

N-methylpyridinium cation. A less reliable value of pK_{R+} at C-2 of this cation is also deduced.

1-Methylnicotinamide Cation (1: W = $CONH_2$)

Martin and Hull[10] measured pK_a = 13.2 for the 1-methylnicotinamide cation in aqueous base. The conjugate base produced in this equilibration does not have an electronic absorption maximum >300 nm, and this clearly rules out any of the possible dihydronicotinamide pseudobases, since 1,2-, 1,4- and 1,6-dihydronicotinamides all display longer wavelength absorption maxima.[11] Martin and Hull persuasively argue that this pK_a value represents ionization of a proton from the C-3 carboxamide group. Brooke and Guttman[12] also propose amide ionization for a similar equilibrium constant which controls the pH-dependence of the kinetics of the hydrolysis of this cation. Thus pK_{R+} for the 1-methylnicotinamide cation must be greater than 13.2. Consistent with this result, a value of pK_{R+} = 14.6 has been deduced[13] for hydroxide ion addition at C-4 of the 1-benzylnicotinamide cation on the basis of the variable kinetic isotope effects observed for the reduction of a variety of quinolinium cations by 1-benzyl-1,4-dihydronicotinamide and its 4,4-dideuterio derivative. This pK_{R+} value has been shown[14] to also accurately predict, via equation [3], the observed second-order rate constant (k_2) for the degenerate transhydrogenation between this cation and its 1,4-dihydro derivative.

$$\log k_2 = -0.56\ pK_{R+} + 5.1 \qquad [3]$$

N-benzyl heteroaromatic cations are more susceptible to nucleophilic addition reactions than the corresponding N-methyl cations. For instance, the association constant (K_{CN}) for cyanide ion addition at C-4 of nicotinamide cations is 13-fold greater (i.e. $\Delta(\log K_{CN}) = 1.1$) for the N-benzyl cation than for the N-methyl cation.[15] A similar substituent effect is also seen in the relative acidities of N-benzyl and N-methyl ammonium cations, which display ΔpK_a in the range 0.7 to 1.3.[16] Using $\Delta pK_{R+} \approx 1.0$ for N-methyl relative to N-benzyl cations, one can then estimate pK_{R+} = 15.6 for the 1-methylnicotinamide cation.

3-Acetyl-1-methylpyridinium Cation (1: W = $COCH_3$)

Martin and Hull[10] measured pK_a = 13.3 for the 3-acetyl-1-methylpyridinium cation. The conjugate base formed in this equilibration displays an absorption maximum at 332 nm (ϵ = 14400 $M^{-1}cm^{-1}$). Although these workers interpreted this result in terms of the addition of hydroxide ion to the pyridinium ring, the regiochemistry of the addition product was not specified. The intensity of this absorption is two- to three-fold greater than normally observed[17] for the longest wavelength absorption maximum in the spectrum of a dihydropyridine

derivative. This observation suggests that this conjugate base may not be a pseudobase produced by hydroxide ion addition to a ring carbon atom of this cation. Johnson and Morrison[18] have suggested that the species that generates this 332 nm maximum is a ring-opened derivative. Such species have been identified for many other pyridinium cations in aqueous base.[2]

Studies of the related 1-methyl-3-phenylacetylpyridinium cation (1:W = $COCH_2C_6H_5$) have identified two acid-base equilibrations other than pseudobase formation in basic aqueous solutions of this cation.[19] The kinetically controlled conjugate base from this species is the hydroxide ion adduct at the carbonyl group (pK_a = 12.31), while thermodynamic control favours the enolate ion formed by deprotonation of the benzylic methylene unit (pK_a = 10.30). Analogous equilibria are possible for the 3-acetyl-1-methylpyridinium cation, which should display a similar susceptibility to hydroxide ion addition to its carbonyl group to that observed for the 3-phenylacetyl cation. The pK_a value for enolate ion formation upon deprotonation of the acetyl group can also be predicted to be in the vicinity of 12 to 13 by analogy to $\Delta pK_a \approx 2.0$ between acetophenone (pK_a = 18.24)[20] and benzyl phenyl ketone ($pK_a \approx 16.1$)[21]. However, one would not expect either the gem diol anion or the enolate ion to have such an intense absorption maximum in the vicinity of 332 nm.

If the interpretation of the conjugate base of λ_{max} = 332 nm as a ring-opened derivative is correct, then the pK_a = 13.3 reported by Martin and Hull is actually a composite equilibrium constant composed of pK_{R+} for pseudobase formation and a ring-opening tautomerization equilibrium constant, and probably also contains contibutions form gem diol anion and enolate ion equilibration with this pyridinium cation.

Equilibrium constants have been reported for a variety of nucleophilic additions to 3-acetylpyridinium and nicotinamide cations. Equilibrium data which allow direct comparisons between these two classes of cations are given in Table 1 for addition of cyanide ion at C-4. As indicated in Table 1, there is general agreement from a number of laboratories, and for a number of different N-substituents in these pairs of cations, that log K_{CN} is approximately 2.2 greater for 3-acetylpyridinium cations than for the correspondingly substituted nicotinamide cations. The relative equilibrium constants for the equilibration of NAD^+ or its 3-acetyl analog with NADH and its 3-acetyl derivative also fit this same pattern. The lone exception in Table 1 is for sulfite ion addition to pairs of pyridinium cations. This difference may be related to the different charge present on the nucleophile and 1,4-dihydropyridine adduct in the case of sulfite ion addition.

This observed $\Delta(\log K_{CN}) \approx 2.2$ in Table 1, can be translated into pK_{R+} being 2.2 lower when a 3-$CONH_2$ substituent is replaced by a 3-$COCH_3$ unit. Thus

pK_{R+} for the 3-acetyl-1-methylpyridinium cation can be predicted to be 15.6 - 2.2 = 13.4

TABLE 1

Equilibrium constants for cyanide ion addition to matched pairs of nicotinamide and 3-acetylpyridinium cations

Reference	No. of cation pairs	Average $\Delta(\log K_{CN})^a$
22	3	2.4
23	1	2.2
24	1	2.1
25	7	2.2
26	1	2.3
27	1	2.3[b]
28	1	3.2[c]

[a]Difference in K_{CN} = $[Py^+][^-CN]/[PyCN]$ for C-4 addition of cyanide ion to pyridinium cations differing in only $COCH_3$ or $CONH_2$ as the C-3 substituent.
[b]K_H for equilibration of NAD^+ (or its 3-acetyl analog) and ethanol with NADH (or its 3-acetyl analog) and acetaldehyde.
[c]K_{SO_3} for C-4 addition of sulfite ion.

A further prediction of pK_{R+} for this cation can be based upon equation [3] and an unpublished value of k_2 = 7.7 x 10^{-3} $M^{-1}s^{-1}$ from our laboratory for the reduction of this cation by 1-benzyl-1,4-dihydronicotinamide in 20% acetonitrile in water at 25° (ionic strength 1.0). Equation [3] predicts pK_{R+} = 12.9, which is in reasonable agreement with the value deduced above, given the uncertainties in each predictive method. These values are both in the vicinity of pK_a = 13.3, originally reported by Martin and Hull[10] for this cation, although for the reasons given above, it seems that this agreement is probably fortuitous. We have taken pK_{R+} = 13.2 for this cation in Table 2, and estimate this to be reliable within ± 0.3 log units.

3-Cyano-1-methylpyridinium Cation (1: W = CN)

The reactions of the 3-cyano-1-methylpyridinium cation in basic aqueous solution are quite complex. Products from disproportionation, ring-opening and the hydration of the nitrile to give the amide have all been reported[29-32], with the predominant product being very dependent upon the solution pH and the cation concentration. There do not appear to be any estimates of pK_{R+} for this

species.

Second-order rate constants are available[33] for the reduction of this cation and its 1-benzyl analogue by 1-benzyl-1,4-dihydronicotinamide to the corresponding 1,4-dihydronicotinonitriles. These rate constants may be used in conjunction with equation [3] for the reduction of pyridinium cations by this reducing agent, to estimate pK_{R+} values for hydroxide ion addition at C-4 of these nicotinonitrile cations. These estimates of pK_{R+} = 12.2 for the 3-cyano-1-methylpyridinium cation and 11.0 for its 1-benzyl analogue, display the expected $\Delta pK_{R+} \approx 1$ for N-methyl and N-benzyl analogues (see above).

In principle one might have expected to predict pK_{R+} for this cation by an analogous method to that which was based upon Table 1 for the 3-acetyl cation. However, there appear to be very few equilibrium constants available for nucleophilic addition to C-4 of nicotinonitrile cations. Wallenfels and Diekmann[24] reported log K_{CN} = 3.256 for cyanide ion addition to the 3-cyano-1-(2,6-dichlorobenzyl)pyridinium cation to give a 1,4-dihydro adduct having λ_{max} = 328 nm. This association constant is unexpectedly slightly smaller than for the corresponding 3-acetyl cation (log K_{CN} = 3.362), and only 2.038 log units larger than for the corresponding nicotinamide cation. Wallenfels and Diekmann show that while a close linear correlation exists between λ_{max} and log K_{CN} for a wide range of pyridinium cations, this 3-cyanopyridinium cation deviates from this correlation quite dramatically. In fact λ_{max} = 328 nm is at somewhat shorter wavelength than expected for this 3-cyano-1,4-dihydropyridine derivative[11], and it seems likely that this equilibrium constant is not a simple expression of cyanide ion addition at C-4 of this cation. A similar reservation must also be held for K_{CN} reported[33] for the 1-benzyl-3-cyanopyridinium cation, and $\Delta(\log K_{CN})$ = 2.6 derived for this cation relative to its 3-$CONH_2$ derivative.

In passing, it is noted that a study is in progress in our laboratory to quantitatively describe the complex reactions[29-32] that 1: W = CN undergoes in aqueous base. We have confirmed from time-dependent electronic spectral observations, that several reactions do occur in these solutions. Although this study is far from complete, it is clear that one of the initial species formed from this cation in aqueous base has λ_{max} = 346 nm, and appears to be related to the cation by a pK_a value of 12.1. These data are consistent with the pK_{R+} value suggested above for this cation.

1-Methyl-3-nitropyridinium Cation (1: W = NO_2)

The thermodynamically controlled pseudobase formed from the 1-methyl-3-nitropyridinium cation (pK_{R+} = 9.42) has an electronic absorption spectrum typical of a 1,4-dihydro-3-nitropyridine derivative.[14] Thus this pK_{R+}

value can be confidently assigned to the C-4 hydroxide ion adduct of this cation.

3,5-Dicyano-1-methylpyridinium Cation

Wallenfels and Hanstein[35] have measured pK_{R+} = 3.8 for the 3,5-dicyano-1-methylpyridinium cation. These workers assigned this value to the formation of a pseudobase (λ_{max} ≈ 350 nm) from hydroxide ion addition at C-2. However, in view of the fact[35] that 3,5-dicyano-1,2-dihydropyridine has λ_{max} = 382 nm, while its 1,4-dihydro isomer displays λ_{max} = 352 nm, it seems more likely that the observed pseudobase species is actually the C-4 hydroxide adduct. As shown below, this interpretation fits well with the other pK_{R+} values assigned for C-4 pseudobase formation in this work.

Linear Free Energy Relationship for C-4 Pseudobase Formation

The pK_{R+} values assigned above to C-4 pseudobase formation in these C-3 substituted 1-methylpyridinium cations are summarized in Table 2.

TABLE 2

pK_{R+} values for C-3 substituted 1-methylpyridinium cations

Substituent	pK_{R+}	σ_p^-	pK_{R+}(calc)[a]	log K_{SO_3}[b]
3-$CONH_2$	15.6	0.62	15.2	-1.2
3-CO_2CH_3		0.74	14.2	-0.3
3-$COCH_3$	13.2	0.84	13.4	2.0
3-CN	12.2	1.00	12.0	3.2
3-NO_2	9.42	1.25	9.9	4.8
3,5-$(CN)_2$	3.8	2.00	3.5	

[a]Calculated from correlation equation [4], using σ_p^- parameters from ref. (36). [b]K_{SO_3} is the association constant for sulfite ion addition to C-4.[28]

Equation [4] shows that these pK_{R+} values are closely correlated with the Hammett σ_p^- substituent constants for the C-3 substituents, where the σ_p^- values are those defined for the ionization of para-substituted anilinium cations. This correlation is expected in view of the resonance stabilization which electron-withdrawing C-3 substituents provide for these 1,4-dihydropyridine pseudobases via resonance contributors such as that shown by 2.

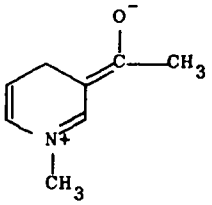
$$pK_{R+} = -8.5\ (\pm 0.4)\ \sigma_p^- + 20.5\ (\pm 0.5) \quad \text{(corr coeff = 0.997)} \quad [4]$$

Analogous close correlations of pK_{R+} with σ_p^- have been previously derived for the C-4 pseudobases of C-3 substituted quinolinium cations (ρ = 8.4)[9] and the C-1 pseudobases of C-4 substituted isoquinolinium cations (ρ = 8.8)[8]. The close correlation indicated by equation [4] and the similarity between the ρ value indicated by this equation, and those found for similarly substituted quinolinium and isoquinolinium cations provide considerable confidence in the pK_{R+} values estimated in the current work. While it is true that equation [3] does assume parallel linear free energy relationships for the 1-benzyl-1,4-dihydronicotinamide reduction of quinolinium and pyridinium cations, it should be noted that the slope ($-\rho$) of the correlation line in equation [4] is determined predominantly by the 3-NO_2 and 3,5-$(CN)_2$ cations for which experimentally measured pK_{R+} values are available.

Table 2 also includes the association constants of Pfleiderer and coworkers[28] for sulfite ion addition to C-4 of these 1-methylpyridinium cations. These data also appear to show a reasonable correlation with σ_p^- (equation [5]), although a poorer fit is obtained than in equation [4]. This poor fit is probably mainly due to experimental error from working with low concentrations of unstable sulfite solutions.

$$\log K_{SO_3} = 9.8\ (\pm 1.4)\ \sigma_p^- - 7.0\ (\pm 1.2) \quad \text{(corr coeff = 0.972)} \quad [5]$$

The only other extensive data on the influence of C-3 substituents upon equilibrium constants for nucleophilic addition at C-4 of pyridinium cations are those of Wallenfels and Diekmann[24] for cyanide ion addition to N-(2,6-dichlorobenzyl) pyridinium cations. These data show so much scatter, that no reliable linear free energy relationship can be deduced, although in passing, it should be noted that Johnson and Smith[37] have shown a linear relationship between $\log K_{SO_3}$ and K_{CN} for nicotinamide cations which differ only in the nature of the substituent on N-1.



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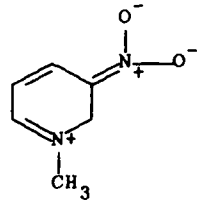

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1-Methylpyridinium cation

Equation [4] predicts pK_{R+} = 20.5 ± 0.5 for pseudobase formation at C-4 of the 1-methylpyridinium cation. This appears to be the first quantitative estimate of this equilibrium constant. As expected, it is significantly larger than pK_{R+} = 17.4 recently deduced[9] for C-4 pseudobase formation by the 1-methylquinolinium cation in aqueous solution.

The estimation of pK_{R+} for pseudobase formation by hydroxide ion addition

at C-2 of the 1-methylpyridinium cation cannot be as confidently attempted at the present time. The only reliable pK_{R+} value at C-2 of a pyridinium cation appears to be 11.6 for the 1-methyl-3-nitropyridinium cation.[14] In this system, the C-2 pseudobase has been established as the kinetically controlled product upon basification of a neutral aqueous solution of this cation, although the thermodynamically more stable pseudobase is the C-4 hydroxide adduct (pK_{R+} = 9.42). An analogous situation exists for the 1-methyl-3-nitroquinolinium cation (pK_{R+} = 6.82 at C-4 and pK_{R+} = 9.16 at C-2).[38] The effect of the 3-nitro substituent is to lower pK_{R+} by 15.4 - 9.16 = 6.2 units relative to the C-3 unsubstituted 1-methylquinolinium cation. Applying this ΔpK_{R+} to pseudobase formation at C-2 in pyridinium cations, and including a statistical factor for the equivalence of the C-2 and C-6 atoms in the 1-methylpyridinium cation, allows the estimation of pK_{R+} = 11.6 + 6.2 - 0.3 = 17.5 at C-2 of this latter cation. This estimate is probably somewhat low, since the resonance contributor 3 is expected to be far more important in the stabilization of the C-2 pseudobase in the pyridine system than the analogous contributor in the quinoline system. This consideration suggests that ΔpK_{R+} for the 3-nitro substituent should probably be somewhat greater for pyridinium cations than for quinolinium cations.

An alternative estimate may be made from the observation[9] that pK_{R+} for pseudobase formation at C-2 of the 1-methylquinolinium cation is 2.0 less than pK_{R+} at C-4 of this cation. Applying this differential to the 1-methylpyridinium cation, and including the statistical factor, leads to pK_{R+} = 20.5 - 2.0 - 0.3 = 18.2 at C-2. This latter value is considered to be the best quantitative estimate that can be made for this parameter at the present time.

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